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Linking Indoor Air and Pharmacokinetic Models to Assess Tetrachloroethylene Risk

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Physiologically based pharmacokinetic (PBPK) models describing the uptake, metabolism, and excretion of xenobiotic compounds are now proposed for use in regulatory health-risk assessments. In this study we investigate the extent of PCE metabolism arising from domestic respiratory exposure to tetrachloroethylene (PCE) from ground water, as predicted using a PBPK model. Indoor exposure patterns we use as input to the PBPK model are realistic ones generated from a three-compartment model describing volatilization of PCE from domestic water into household air. Values we use for the metabolic parameters of the PBPK model are estimated from data on urinary metabolites in workers exposed to PCE. It is shown that for respiratory PCE exposure due to typical levels of PCE in ground water, use of time-weighted average air concentrations with a steady-state PBPK model yields estimates of total metabolized PCE similar to those obtained using completely dynamic modeling, despite considerable uncertainty in key exposure- and metabolic-model parameters. These findings suggest that, for PCE, risk estimation taking pharmacokinetics into account may be accomplished using a simple analytic approach.

KEY WORDS: Tetrachloroethylene; indoor respiratory exposure; pharmacokinetic models; uncertainty.

1. INTRODUCTION

Multicompartment models known as physiologically based pharmacokinetic (PBPK) models are used increasingly in health-risk assessment for volatile organic compounds (VOCs). These models predict the uptake, metabolism and excretion of such chemicals in exposed animals or people. In current applications of such models, however, input has consisted of simplistic exposure scenarios that often do not represent realistic environmental exposure conditions of regulatory concern. Recent studies have shown that exposure to VOCs in drinking-water supplies can result not only from direct ingestion of contaminated water, but also from inhalation and dermal absorption.[1-3] McKone has shown that daily personal exposure to VOCs from tap water through inhalation can range from 1.5 to 6.0 times the exposure attributable to ingestion of 2 liters/d of water.[4] This daily exposure is dominated by large, short-term exposures during specific activities such as showering or bathing and time spent in bathrooms. One question raised by this observation is whether the metabolized dose is sensitive to the temporal exposure pattern. To address this question, we explored how realistic scenarios for indoor respiratory exposure to tetrachloroethylene (PCE) from ground water affect the extent of PCE metabolism, as predicted by a PBPK model. We focused on the degree to which

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dynamic, as opposed to steady-state, modeling is actually necessary to predict PCE metabolism, and on whether conclusions in this regard are significantly affected by uncertainty in estimates of parameters that govern PCE metabolism in humans.

To place our analysis in the context of risk assessment, we note that PCE has been shown to cause tumors in rodents and is considered to be a suspected human carcinogen for purposes of environmental regulation.[5] At very low doses of environmental concern, a conservative risk-assessment approach widely in use views the carcinogenic risk posed by PCE as an approximately linear function of the amount of this compound that is metabolized.[5-7]

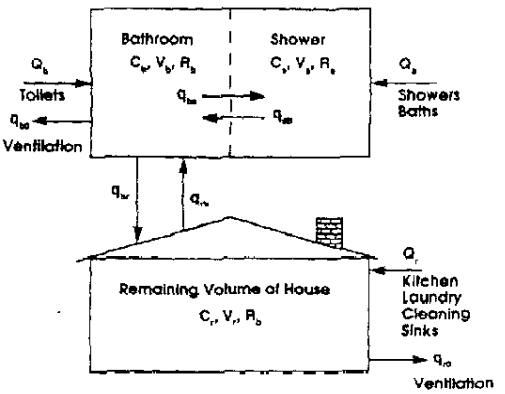

Fig. 1. A three-compartment model for simulating the transfer of volatile organic compounds from tap water to indoor air.

2. METHODS

Predictions of indoor respiratory exposure to PCE and of PCE pharmacokinetics were made using the mass-balance models described below. Analytic treatment of the PBPK model at steady state is reported in Section 3. The PBPK model was fitted to two sets of available data on PCE metabolism in humans occupationally exposed to PCE, and the resulting estimates for model parameters governing metabolism are used with other information for a simple analysis of current uncertainty in the extent to which humans metabolize PCE.

2.1. A Three-Compartment, Mass-Balance Model for Indoor Respiratory Exposure

To model indoor respiratory exposure, we used a three-compartment model that simulates the transfer and distribution of VOCs inside homes.[4] The three compartments in this model are the shower/bath stall, the bathroom, and the remaining household volume. Figure 1 illustrates the major components of the model and shows the mass-flow pathways that are addressed in the model.

The mass-balance equations for the three compartments are

$$V_s\dot{C}_s = Q_s + q_{bs}C_b - q_{sb}C_s \qquad \text{(shower stall)} \quad (1)$$

$$V_b\dot{C}_b = Q_b + q_{sb}C_s + q_{rb}C_r - (q_{bs} + q_{bo} + q_{br})C_b \qquad \text{(bathroom)} \quad (2)$$

$$V_r\dot{C}_r = Q_r + q_{br}C_b - (q_{rb} + q_{ro})C_r \qquad \text{(remainder of the house)} \quad (3)$$

In these equations, the C's, V's, Q's, and q's refer to concentrations in mg/liter volumes in liters, sources in mg/min, and air-exchange rates in liters/min, respectively. For notational convenience, the dependence of the state variables (C's and Q's) in this model on time, t, is suppressed, and dot notation is used to represent differentiation with respect to time (e.g., $\dot{C}_s = dC_s/dt$). The subscripts s, b, and r are used to indicate the shower, bathroom, and remaining household compartments, respectively, while o denotes outside air. In Fig. 1, the subscripted R's represent the residence time of air mass in each compartment. The air-exchange parameters, q, and the parameters V_s, V_b, V_r, R_s, R_b, and R_r are taken from and summarized in a report by McKone, where representative values and value ranges are provided.[4]

The source terms Q_s, Q_b, and Q_r are used to account for the input of a VOC from the use of contaminated water in each respective household compartment. Because we were not interested in estimating total PCE concentration indoors but only the concentration attributable to contaminated water supplies, the concentration of PCE in ambient air (which in general is <10 ppb[5]) was ignored.

Daily concentration profiles obtained for C_s, C_b, and C_r demonstrate that the concentration in all three compartments is driven largely by the shower source, and that individual exposure (concentration $\times$ time) occurs predominantly in that compartment. We calculated two sets of 24-h concentration profiles: a "reference" profile (based on a set of typical values assigned to the model parameters) and an

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"upper bound" profile (obtained by assigning conservative values to the model parameters).[4] To calculate daily average time-dependent concentration profiles of human exposure, we used the following expression:

$$C_{in} = F_s C_s + F_b C_b + F_r C_r \qquad (4)$$

in which C_{in} (mg/liter) is personal air concentration at time t and F_s, F_b, and F_r are (unitless) occupancy factors representing the probability that an individual is in the shower, bathroom, or remaining household, respectively, at time t. However, to derive dynamic input for pharmacokinetic modeling in the present study, we set F_s equal to one and used the actual time-dependent PCE concentration profile for an individual in the shower where the highest exposures occur (see below), and we ignored the other two minor sources of indoor exposure. Dynamic simulations using the exposure model were carried out by simultaneous numerical integration of the sets of differential equations involved, using the PREMOD/MODAID computer program for dynamic systems simulation.[8]

A daily concentration profile for PCE in personal air is illustrated in Fig. 2 for an individual who takes a 10-min shower using 75 liters of tap water, spends an additional 15 min in the bathroom after the shower, spends 24 h/d in the home, and makes three additional 5-min visits to the bathroom. In this calculation, the PCE concentration in the water supply was taken to be 1 mg/liter. The average personal-air concentration derived from Fig. 2 is 4.0×10^{-4} mg/liter (0.058 ppm), and the corresponding peak concentration in the shower is about 0.1 mg/liter (15 ppm). The "reference" conditions we considered for adult bathing and housing activity assumed one 10-min shower per day using 75 liters of water plus 40 min/d in the bathroom and 12 h outside the house (where no exposure was assumed). The "upper bound" conditions we considered for adults assumed one 20-min shower per day using 75 liters of water plus 40 min/d in the bathroom and no time outside the house. Both "reference" and "upper bound" showering conditions were assumed to involve four consecutive showers per household-day, using a total of 300 liters of water.[4]

Using the household exposure model described, it has been estimated that for 1 mg/liter in the water supply, the daily average concentration of PCE in personal air ranges from 3.0×10^{-4} mg/liter (0.044 ppm, the reference case) to 6.0×10^{-4} mg/liter (0.088 ppm, the upper-bound case), with the peak shower concentration ranging from 0.02 mg/liter (3.0 ppm) to 0.03 mg/liter (4.4 ppm).[4] These predicted concentrations of PCE in air may be linearly scaled to reflect an actual concentration of PCE in tap water. For example, a survey of 869 of 1426 wells in 79 large water-supply systems serving 7.2 million people in California revealed that water from 199 of the tested wells contained PCE at concentrations up to 166 μg/liter, with a median concentration of 1.9 μg/liter.[9,10] A survey of PCE concentration in 1102 surface water measurements in 45 states yielded a mean value of 1 μg/liter.[5] Using the highest measured concentration of 166 μg/liter as input to the

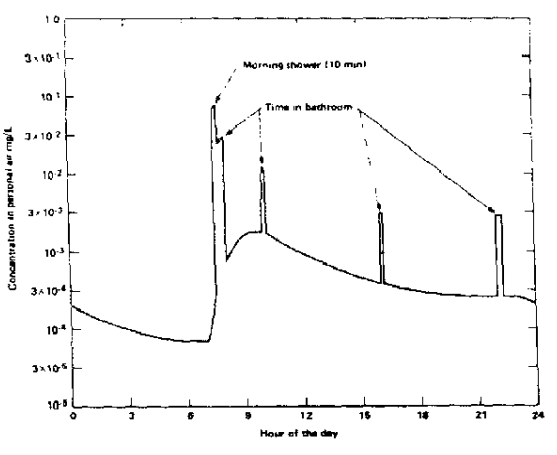

Fig. 2. Concentration profile of PCE in personal air derived from the indoor exposure model.

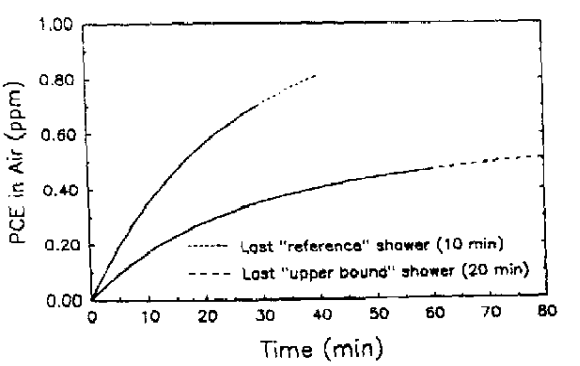

Fig. 3. Concentration of PCE in shower-stall air over time predicted by the indoor exposure model, assuming each shower uses 75 liters of tap water containing 166 μg PCE/liter.

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indoor exposure model described, we predicted peak air concentrations in a shower stall, during the last of four consecutive showers, to be less than 1 ppm (Fig. 3).

2.2. PBPK Model for PCE

The pharmacokinetic model used here was developed by Ramsey and Andersen to describe the uptake, metabolism, and excretion of styrene in rats and humans.[11] The structure of the model is shown in Fig. 4, and its parameter definitions are given in Table I. This type of model has been applied to the study and prediction of the pharmacokinetics of other VOCs in animals and humans[12-14] and to investigate PCE pharmacokinetics in particular.[6,15-17] The model consists of a set of differential equations that describe the rate of change of the amount of absorbed chemical present in each of four physiologically realistic tissue compartments, which are assumed to be ideally well mixed at any given time. Here we consider chemical input only via the inhalation route, but dermal and ingestion input routes are readily incorporated into the model. Metabolism is presumed to occur in the liver through a saturable enzymatic path with Michaelis–Menten kinetics.

According to the model, pulmonary uptake of a chemical occurs continuously such that alveolar concentration, C_a, is in instantaneous equilibrium with arterial blood governed by the blood/air partition coefficient, P_b, in accordance with the relation $C_a = B_a/P_b$. Similarly, the concentrations, C_i, of chemical in each tissue compartment are presumed to be in instantaneous equilibrium with the concentrations, B_i, in venous blood exiting the corresponding tissue,

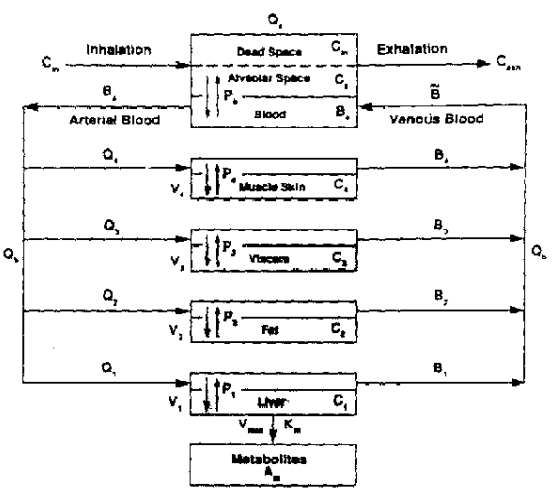

Fig. 4. Ramsey–Andersen physiologically based pharmacokinetic (PBPK) model for inhalation of volatile organic compounds. The model assumes that four "well-stirred" tissue compartments collect or release a compound at rates governed by air concentration, air and blood flows, blood concentrations, compartment volumes, tissue/blood partition coefficients, and metabolism. (See Table I for definition of model parameters.)

Table I. Compartment and Parameter Definitions for the Ramsey–Andersen PBPK Model[a]

Abbreviation	Definition	Unit
C_{in}	Concentration in air inhaled	mg/liter air
C_a	Concentration in alveolar air	mg/liter air
C_{exh}	Measured concentration in expired breath	mg/liter air
Q_a	Alveolar ventilation rate	liter air/h
Q_b	Cardiac output	liter blood/h
P_b	Blood/air partition coefficient	liter air/liter blood
B_a	Arterial blood concentration	mg/liter blood
$\bar{B}$	Venous blood concentration	mg/liter blood
A_m	Amount metabolized in liver	mg
Q_i	Blood flow rate to compartment i (where $\sum Q_i = Q_b$)	liter blood/h
V_i	Volume of compartment i	liter ($\cong$ kg)
C_i	Concentration in compartment i	mg/liter
B_i	Concentration in venous blood leaving compartment i	mg/liter blood
A_i	Amount in compartment i	mg
P_i	Tissue/blood partition coefficient for compartment i	liter blood/liter tissue i
V_{max}	Maximum metabolic rate	mg/h
K_m	Michaelis constant = $\{B_1 \mid (dA_m/dt = V_{max}/2)\}$	mg/liter blood

[a] Compartmental subscripts: $i = 1$, Liver (metabolizing tissue group); 2, fat tissue (very poorly perfused); 3, richly perfused tissues (brain, kidney, viscera); 4, poorly perfused tissues (muscle, skin).

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governed by the corresponding tissue/blood partition coefficients such that $B_i = C_i/P_i$. The amount of chemical in any given tissue compartment is given by $A_i = C_i V_i$. Again, the dependence of state variables (C's, B's, and A's) on time, t, is suppressed, and dot notation is used to represent differentiation with respect to time.

In any given interval, dt, a VOC delivered to the lung via respiratory retention and via returning venous blood is balanced in this model by the chemical mass exiting the lung via exhalation and via arterial blood, such that

$$\left(Q_a C_{in} + Q_b \bar{B}\right) dt = \left(Q_a C_a + Q_b B_a\right) dt$$

or

$$Q_a\left(C_{in} - C_a\right) = Q_b\left(B_a - \bar{B}\right)$$

which, recalling that $C_a = B_a/P_b$, yields

$$B_a = \frac{Q_a C_{in} + Q_b \bar{B}}{(Q_a/P_b) + Q_b} \tag{5}$$

[An experimentally measured concentration in exhaled breath is given by $C_{exh} = F_d C_{in} + (1 - F_d)C_a$, where the dilution factor F_d approaches zero as the efficiency of measuring purely alveolar expired air approaches 100%.] Equation (5) specifies B_a (and thus C_a and C_{exh}) to be at each instant a flow-weighted average of C_{in} and $\bar{B}$. Similarly, the concentration $\bar{B}$ in venous blood returning from each compartment is presumed to be the instantaneous flow-weighted average

$$\bar{B} = \frac{1}{Q_h} \sum_{i=1}^{4} Q_i B_i \tag{6}$$

For the nonmetabolizing tissues, the amount $Q_i B_a\, dt$ of chemical entering the ith compartment via arterial blood during any given interval dt is set equal to the amount dA_i gained by that compartment plus the amount $Q_i B_i\, dt$ leaving in venous blood, for $i = 2, 3, 4$. The chemical concentration for each of these compartments is therefore defined by the state equation

$$\dot{B}_i = \frac{Q_i}{V_i P_i}\left(B_a - B_i\right), \qquad i = 2, 3, 4 \tag{7}$$

The rate of chemical metabolism in liver is given by the Michaelis–Menten relation

$$\dot{A}_m = \frac{V_{max} B_1}{K_m + B_1} \tag{8}$$

in which K_m is defined as the concentration in venous blood from liver (or, alternatively, $K_m P_1$ is the chemical concentration in liver) at which the liver's metabolic velocity $\dot{A}_m$ is half its maximum value, V_{max}. Thus, the state equation for venous liver-blood concentration is given by

$$\dot{B}_1 = \frac{Q_1}{V_1 P_1}\left(B_a - B_1\right) - \frac{\dot{A}_m}{V_1 P_1} \tag{9}$$

The system of Eqs. (6–9) represents the PBPK model for inhalation of a VOC, and for any given time its compartmental amounts A_i, or corresponding concentrations C_i or B_i, are found by simultaneous numerical integration of the system.

Of particular interest in the context of risk assessment is the metabolized fraction of the total quantity of chemical potentially available through alveolar ventilation for absorption and metabolism. Under steady-state conditions, the corresponding quantity of interest is the fraction, f_m, of the maximum plausible metabolic rate, given C_{in}:

$$f_m = \dot{A}_m/(Q_a C_{in}) \tag{10}$$

The value f_m calculated from the PBPK model may be contrasted with the assumption, sometimes made in the context of carcinogen risk assessment,[7] that 100% of a chemical entering the lungs through total respiratory ventilation (or that contained in approximately 20 m^3/d for a reference 70-kg man) is absorbed and potentially available for metabolism.

2.3. PBPK Model for PCE Metabolism in Occupationally Exposed Humans

The Ramsey–Andersen PBPK model described above was adapted, as described below, in order to fit data of Ikeda *et al.*[18,19] and Ohtsuki *et al.*[20] on urinary metabolites produced by Japanese workers exposed to PCE. These two studies are the only ones available in which metabolites were measured in humans over sustained exposure periods. The Ikeda *et al.* data are based on surveys of workplace air and urine samples of 34 males in 7 workshops where PCE was present in air at 8-h time-weighted average (TWA) concentrations ranging from 0 to 400 ppm, and where workshop-specific concentrations were re-

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ported to be relatively constant over the common 8-h/d, 6-d/wk occupational schedule of the workers studied.[18] Urine samples were passed at about 1:00 p.m. in the "latter half" of the week.[18] Concentrations of the PCE metabolites trichloracetic acid (TCA), trichloroethanol, and total trichloro-compounds (TTC) in urine (adjusted to a specific gravity of 1.016) were measured for each worker along with a corresponding TWA concentration of PCE in air.

The Ohtsuki *et al.* data considered here are based on surveys of urine samples and PCE in personal workplace air of 20 males employed in several dry-cleaning shops and 16 males engaged in removing dye-repellent glue from silk in a kimono-production shop; in all of the shops PCE was used as the solvent.[20] TTC concentrations were measured in samples of end-of-shift urine (adjusted to a specific gravity of 1.016), and measured TWA concentrations of PCE in personal air ranged up to 630 ppm. Otherwise, the exposure scenario for the workers in this study was the same as that in the Ikeda *et al.* study.

The values we used for the parameters listed in Table I pertaining to a reference, 70-kg male worker are given in Table II. These parameter values were used by Ward *et al.*[17] in a similar analysis of the Ikeda *et al.* data on PCE metabolism in humans; the partition coefficients P_b and P_i were obtained experimentally using human blood and animal tissues.[13]

We assumed that a reference 70-kg male produces an average of 0.0583 liters urine per hour during the day, or a total of 1.4 liters/d.[21] We also assumed, in the absence of more specific data, that urine samples were passed at 1:00 p.m. and 5:00 p.m. by all the workers studied by Ikeda *et al.*, respectively, on Thursdays, Fridays, and Saturdays of each week, and that a prior urination (emptying the bladder) occurred 4 h before samples were passed on each collection day for all workers. It was further assumed that for 70-kg males, all PCE metabolites, reflected by measured concentrations of TTC in urine, were removed exponentially from blood to collect in urine with a rate constant of 0.0137 h^{-1}, based on the assumption that TCA is the primary PCE metabolite in urine[5] and on data indicating that blood concentration of TCA in (TCA-dosed) humans decreases exponentially with a half-life of 50.6 h.[22]

For the purpose of modeling the occupational exposures considered here, we scaled the reference values given in Table II to approximate those applicable to a typical Japanese male worker. To this end, body weight was set at 55.2 kg and the tissue vol-

Table II. Parameter Values Used in PBPK Model for PCE

Parameter	Unit	Reference male human[a]	Japanese male worker[b]
W (body weight)	kg	70	55.2
Q_a	liter/h	353.5[c]	299.3
Q_b	liter/h	371.6	314.7
P_b		10.3	10.3
Q_i/Q_b $i=1$		0.25	0.25
2		0.05	0.04
3		0.51	0.52
4		0.19	0.19
V_i/W $i=1$		0.04	0.027
2		0.20	0.15
3		0.05	0.10
4		0.62	0.61
P_i $i=1$		6.82	6.82
2		159	159
3		6.82	6.82
4		7.77	7.77

[a] Physiological parameter values taken from Ward *et al.*[17]; values for partition coefficients are based on gas uptake experiments.[13]

[b] Parameter values are scaled from those corresponding to reference male human, based on the anatomical model of Kerr[23] for reference Japanese adults.

[c] This value represents, e.g., an average daily alveolar ventilation rate for a 70-kg male assuming that alveolar volume is 50% of total lung capacity, that 84% of tidal volume is available for mixing with alveolar air (corresponding to a dead space of 160 ml and an average tidal volume of 1 liter), and that total respiratory volume is approximately 20 m^3/d.[21]

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umes, V_i, were adjusted to the new values shown in Table II, based on an anatomical model developed specifically for Japanese adults.[23] The values for the blood-flow fractions Q_2/Q_b and Q_3/Q_b were changed slightly to reflect the altered tissue volumes. The reference flow rates Q_a and Q_b and that for urinary output were all decreased by the factor $(55.2/70)^{0.7}$, and the reference rate constant for metabolite clearance to urine from a given volume of blood was increased by the factor $(70/55.2)^{0.3}$, in accordance with the assumption that physiological parameters vary with basal metabolic rate in approximate proportion to the body surface area.[6,11,12]

To approximate conditions of dynamic equilibrium, the occupational exposure scenario was run for a simulated 5-wk period. Workers were assumed to be exposed to TCE from 8:00 a.m. to 12:00 noon and 1:00 p.m. to 5:00 p.m. on Monday through Saturday of each week. Calculated urinary concentrations of TTC on each of the 3 urine-collection days in the fifth week of the simulation were averaged to yield a predicted urinary metabolite concentration corresponding to any given values for the input parameters C_i, V_{max}, and K_m. Urinary metabolite concentrations were expressed in mg/liter of TTC as TCA, as was done in the Ikeda *et al.* and Ohtsuki *et al.* studies,[18-20] which approximates the unit of mg/liter PCE because the molecular weights of PCE and TCA are approximately equal. Numerical integration of the system of differential equations involved was performed on a VAX 11/750 computer using a variable-step Gear method.[24] Optimization of the metabolic parameters was determined by least-squares fit of PBPK-simulated data to the empirical data from each of the two studies considered, using a gradient-grid approach.

2.4. Metabolic Parameter Uncertainty

The existence of alternative sets of data on PCE metabolism in humans and animals allowed us to perform a crude analysis of uncertainty associated with our PBPK-based estimates of V_{max} and K_m. The human data were used directly to provide two, study-specific, alternative estimates of K_m. Corresponding estimates of V_{max} were first multiplied by the factor $(70/55.2)^{0.7}$ to scale the rate parameter to apply to a reference 70-kg human (see Section 2.3), and then multiplied by an "excretion factor" (f_e) to account for nonurinary PCE metabolites in humans. In the absence of quantitative information on the extent to which humans metabolize PCE to nonurinary metabolites, estimation of f_e was based on the data available for mice and rats[25-29] summarized in Table III. On the basis of this animal data, it is reasonable to assume that it is unlikely that less than a third of metabolized PCE would be excreted in the

Table III. PCE Metabolism to Products Excreted in Urine by Mice and Rats

Species (sex)	Strain	Total applied dose or concentration	Metabolites (mg/kg)	Metabolites in urine as a percent of total metabolites (%)	Reference
Mice (M)	B6C3F1	500 mg/kg[a]	85.0	82.8	(25)
		10 ppm-6 h[b]	14.8	79.8	
Mice (M)	B6C3F1	900 mg/kg[c]	200	64.6	(26)
Mice (F)	NMRI	800 mg/kg[a]	87.2	66.1	(27)
Rats (M)	Sprague-Dawley	1 mg/kg[a]	0.28	57.1	(28)
		500 mg/kg[a]	51.0	45.7	
		10 ppm-6 h[b]	1.87	58.9	
		600 ppm-6 h[b]	36.4	49.9	
Rats (M)	Sprague-Dawley	8.1 mg/kg[d]	0.98	61.0	(29)
Rats (M)	Osborne-Mendel	1000 mg/kg[c]	23.9	46.9	(26)
Rats (F)	Wistar	800 mg/kg[a]	61.6	31.2	(27)

[a] Single gavage dose of radio labeled PCE in corn oil vehicle.
[b] Single 6-h respiratory exposure to radiolabeled PCE.
[c] Single gavage dose of radiolabeled PCE in corn oil vehicle, after similar dosing with unlabeled PCE for 4 wk, 5 d/wk.
[d] Administered in drinking water (approximately 150 ppm PCE) for 12 h.

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form of urinary products in humans, but that this amount might be as high as 100%. We used the midpoint of this range as our best estimate, so that in this analysis $f_e = 1.5$ (range: 1.0–3.0).

3. RESULTS

3.1. Analysis of the Steady-State PBPK System

For this PBPK system using the reference parameter values listed in Table II, steady-state conditions are approximately attained with constant PCE input after roughly 10 to 15 d. Because at steady state $B_a = B_i$ for $i = 2,3,4$, Eq. (6) reduces to

$$\bar{B} = \frac{1}{Q_b}[Q_1 B_1 + B_a(Q_b - Q_1)] \quad (11)$$

so that Eq. (5) reduces to

$$B_a = \frac{Q_a C_{in} + Q_1 B_1}{(Q_a/P_b) + Q_1} \quad (12)$$

Also at steady state, Eq. (9) reduces to the form

$$\frac{V_{max} B_1}{K_m + B_1} = Q_1(B_a - B_1) \quad (13)$$

so that the solution for venous liver blood concentration, given input C_{in}, is the quadratic root

$$B_1 = Y + (Y^2 + Z)^{1/2} \quad (14a)$$

in which

$$Y = \frac{1}{2}\left[C_{in}P_b - V_{max}\left[\frac{P_b}{Q_a} + \frac{1}{Q_1}\right] - K_m\right] \quad (14b)$$

and

$$Z = K_m P_b C_{in} \quad (14c)$$

The steady-state metabolic rate is thus given by using Eqs. (14a)–(14c) to evaluate B_1 in Eq. (8), and likewise in the expression for the fraction f_m of maximal metabolic rate for PCE given by Eq. (10). Of greater interest in the context of environmental risk assessment is the limiting value of f_m that is approximated at very low exposure levels that might be typical of nonoccupational respiratory exposure to PCE. It can be shown that this limiting value is given by

$$f_m^* = \lim_{C_{in} \to 0} f_m = \left[\frac{Q_a}{P_b}\left(\frac{K_m}{V_{max}} + \frac{1}{Q_1}\right) + 1\right]^{-1} \quad (15)$$

Also of interest is the maximally conservative assumption that infinite metabolism is approached as steady state $C_{in} \to 0$, yielding the new limit

$$f_m^{**} = \lim_{V_{max} \to \infty} f_m^* = \left[\frac{(Q_a/Q_1)}{P_b} + 1\right]^{-1} \quad (16)$$

representing the physiologically determined upper bound on the fraction of intake capable of being metabolized. This limiting value is a function of just three physiological parameters, only one of which is influenced by the particular chemical under consideration. For PCE, using the parameter values given in Table II, f_m^{**} equals 0.73 and is invariant with respect to body weight.

3.2. Metabolic Parameter Estimation

The relationships between the predicted concentration of PCE in urine and PCE concentration in workplace air based on our PBPK simulations for the workers from the Ikeda *et al.* and Ohtsuki *et al.* studies are shown in Figs. 5 and 6, respectively, along with the corresponding best-fit values for V_{max} and K_m. The values 0.19 and 6.1 mg/liter were used directly to reflect a range of uncertainty in K_m, whereas the estimates for V_{max} were scaled as described in Section 2.4 to yield the corresponding best-estimate (range) values of 4.1 (2.7 to 8.2) mg/h and 12 (8.3 to 25) mg/h, respectively, for V_{max} based on the two studies considered.

3.3. Impact of Metabolic Parameter Uncertainty at Steady State

The relationship between C_{in} and f_m, based on Eqs. (10), (14a)–(14c), and (15) and on the estimates of V_{max} and K_m we obtained for a reference 70-kg adult, is shown in Fig. 7. This figure illustrates how the 30-fold range of uncertainty obtained for the ratio V_{max}/K_m (1.4–43 liters/h) translates into a 12-fold range of uncertainty in the low-dose metabolic limit, f_m^* (0.038–0.45). Taking this uncertainty into account, we estimated f_m^* to be between 5% and 65%

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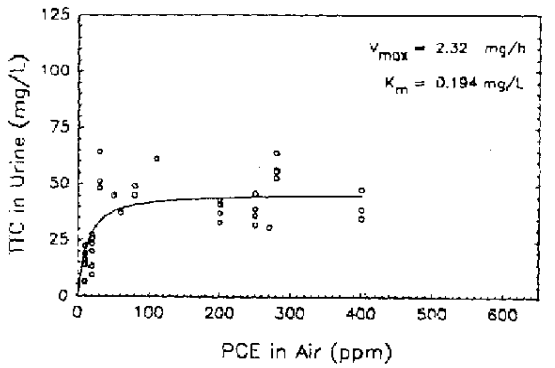

Fig. 5. Least-squares estimates of V_{max} and K_m obtained by fitting the output of a PBPK model (solid curve) to data (○) of Ikeda *et al.*[18,19] on human metabolism of PCE to total trichloro-compounds (TTC) measured in urine (adjusted to a specific gravity of 1.016) at different occupational exposure levels.

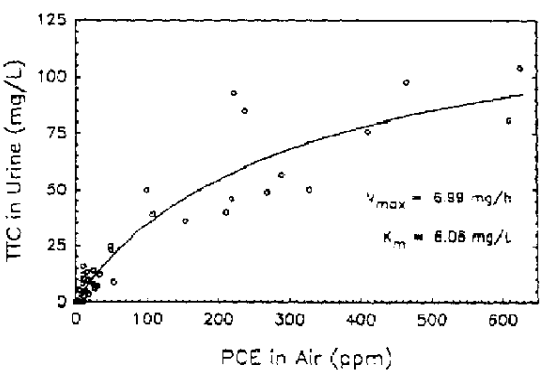

Fig. 6. Least-squares fit of V_{max} and K_m obtained by fitting the output of a PBPK model (solid curve) to data (○) of Ohtsuki *et al.*[20] on human metabolism of PCE to total trichloro-compounds (TTC) measured in urine (adjusted to a specific gravity of 1.016) at different occupational exposure levels.

of its upper physiological bound, f_m^{**}, defined by Eq. (16).

Figure 7 also clearly illustrates that it may be very misleading to generalize about human capacity to metabolize very low doses of PCE on the basis of data on urinary metabolites produced by humans experimentally exposed to PCE for short periods at relatively high (>10 ppm) concentrations in air. It has been inferred from such experimental studies that f_m^* ranges from 2% to 4%,[5,20,30,31] whereas we, using an analytic PBPK approach, and other investigators,[6,16] using a numerical PBPK approach, have shown that f_m^* may actually be greater by a factor of 10–20.

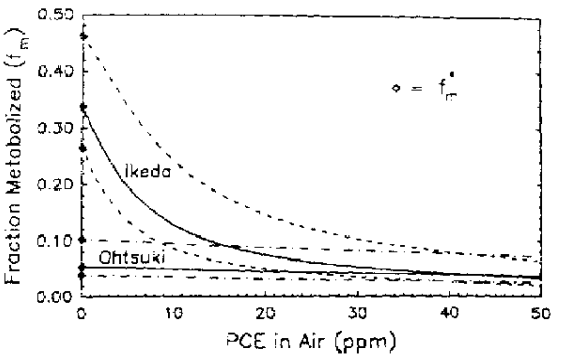

Fig. 7. Relation of the metabolized fraction (f_m) of respired PCE to alternative constant PCE concentrations in air and alternative metabolic parameter values, as predicted by the PBPK model for a "reference" 70-kg male. Solid curves (——) labeled "Ikeda" and "Ohtsuki" assume that the parameters (V_{max}, K_m) are best estimated by (4.1 mg/h, 0.19 mg/liter) and (12 mg/h, 6.1 mg/liter) based on the data of Ikeda *et al.*[18,19] and Ohtsuki *et al.*,[20] respectively. The corresponding lower and upper bounds on f_m shown as dashed curves (– – – for Ikeda, – · – · for Ohtsuki) assume that V_{max} is 2/3 and 3/2 of its corresponding best estimate, respectively.

3.4. PCE Metabolism Due to Indoor Exposure

Under time-varying exposure conditions, Eq. (8) implies that when varying air concentrations remain very small, such that $B_1 \ll K_m$ at all times, the average metabolic rate $\bar{A}_m$ over a given exposure period T is approximated by the value $\tilde{A}_m = (V_{max}/K_m)\bar{B}_1$, where $\bar{B}_1$ is the time-weighted average (TWA) value of B_1 over that period. Let $\max(B_1)$ denote the maximum value of B_1 attained over an exposure period T. If a dynamic input concentration $C_{in}(t)$, for $0 < t < T$, is such that produces $\max(B_1) \leq K_m$, then it follows that

$$\left(\bar{A}_m/\tilde{A}_m\right) \leq \left(1 + [\max(B_1)/K_m]\right)^{-1} \qquad (17)$$

i.e., that metabolism is approximately linear [to within a factor of 2, or, e.g., to within 10% if $\max(B_1) \leq 0.1K_m$]. In the case that $\max(B_1)$ due to a constant input C_{in} pulsed for a time $\tau \ll T$ is much greater than K_m, then this exposure must result in a lower metabolized dose than that arising from an "equivalent" TWA exposure $\bar{C}_{in}T = C_{in}\tau$ over the longer averaging period T whenever $[\max(B_1)|\bar{C}_{in}] \ll K_m$,

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simply because when metabolism is more highly saturated, a greater percent of total respired dose is exhaled and hence excluded from potential metabolism.

To determine whether nonlinear metabolism is relevant at the levels of inhalation exposure associated with PCE concentrations in public water supplies, we simulated PCE metabolism in a reference 70-kg adult taking the last of four consecutive showers, using the two air concentration patterns shown in Fig. 3 as inputs to the PBPK model. The dashed curves in Fig. 8 show the corresponding increases in B_1 with time under the assumption that $V_{max} = 2.7$ mg/h and $K_m = 0.19$ mg/liter, which represents that set of values, among the six sets obtained earlier (see Fig. 7), generating the largest final value of the ratio B_1/K_m. Even under the conservative assumptions used here regarding PCE concentration in household water (0.166 mg/liter) and metabolic parameter values, Fig. 8 reveals that B_1 attains less than 2% of the corresponding value of K_m, ensuring that virtually linear metabolism occurs in the context of domestic respiratory exposure to PCE.

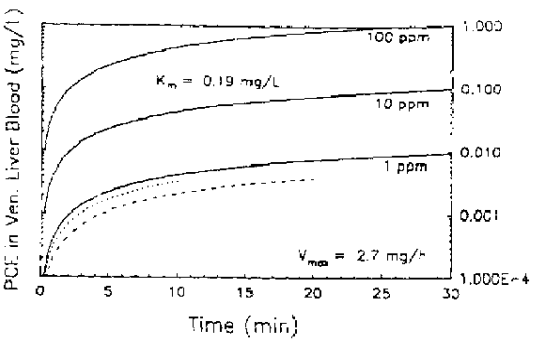

Fig. 8. PCE concentration (B_1) in venous liver blood over time in response to exposure to the two different PCE concentrations in air associated with the "reference" and "upper bound" estimates of shower exposures shown in Fig. 3, as predicted by a PBPK model using parameter values for a "reference" 70-kg male and the values of V_{max} and K_m shown. Also shown, for comparison, are the increases in B_1 predicted to result from continuous respiratory exposure to 1, 10, and 100 ppm PCE in air.

4. DISCUSSION

The estimates of reference parameter values governing PCE metabolism in humans that we obtained are compared in Table IV with corresponding estimates from two earlier studies. Our analysis of the Ikeda *et al.*[18] data yielded a lower estimate of K_m than corresponding values reported by Hattis *et al.*[16] and Ward *et al.*,[17] who analyzed the same data, resulting in a V_{max}/K_m ratio about twice that reported in these two studies. Our analysis of the Ohtsuki *et al.*[20] data yielded estimates similar to those reported by Hattis *et al.*[16]

Details of procedures used by Ward *et al.*[17] were not provided in their study. The metabolic parameter estimation procedure used by Hattis *et al.*[16] was only semiquantitative, and they used

Table IV. Estimates of Parameter Values Governing PCE Metabolism in a Reference 70-kg Male

Parameter	Human data source	Study: Hattis *et al.*[16]	Study: Ward *et al.*[17]	Study: Bogen and McKone[a]
V_{max} (mg/h)	Ikeda *et al.*[18]	6.2	3.5	4.1 (2.7–8.2)
	Ohtsuki *et al.*[20]	9.0	ND[b]	12 (8.3–25)
K_m (mg/liter)	Ikeda *et al.*[18]	0.61	0.30	0.19
	Ohtsuki *et al.*[20]	5.7	ND	6.1
V_{max}/K_m (liter/h)	Ikeda *et al.*[18]	10	12	23 (14–43)
	Ohtsuki *et al.*[20]	1.6	ND	2.0 (1.4–4.1)

[a] Estimated range of uncertainty indicated by values in parentheses.
[b] ND = analysis not done.

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simulated occupational exposure periods of only up to 2 wk despite their modeling results indicating that dynamic equilibrium for PCE metabolism was not achieved within that period. In contrast, for metabolic parameter estimation we used a least-squares fit of our PBPK model to the complete sets of available data on PCE metabolism in occupationally exposed humans using a 5-wk simulated exposure period. Hattis *et al.*[16] used a more realistic physiological model than ours in that diurnal changes in breathing rate and blood flows were incorporated, whereas ours reflected daily averages; however, with regard to urinary output our model is physiologically more realistic than the averaging approach taken by Hattis *et al.*[16] In addition, Hattis *et al.*[16] used values of P_l and P_b that were somewhat lower and higher, respectively (which tends to cancel out the effect of this difference), than those used by us and by Ward *et al.*[17] Differences in modeling approaches such as those reviewed here clearly may affect metabolic parameter estimates obtained. Nevertheless, the general similarity of results obtained in three different studies is reassuring.

Steady-state analysis of the PBPK model used here provides several simple relationships that are directly relevant to environmental risk assessment for VOCs subject to metabolism. In particular, it provides an upper bound on the amount of inhaled chemical that is capable of being metabolized. We have further demonstrated that, for respiratory PCE exposure at indoor air concentrations arising from typical levels of PCE contamination in well water, metabolized dose can conveniently be approximated using estimated TWA air concentrations of PCE with a PBPK model under steady-state assumptions, despite the large temporal fluctuations in air concentration associated with a realistic indoor exposure scenario and the large degree of uncertainty in parameter estimates for PCE metabolism in humans.

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